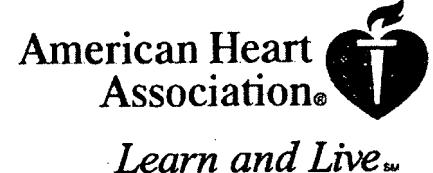


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Diuretics and Risk of Arrhythmic Death in Patients With Left Ventricular Dysfunction

Howard A. Cooper, MD; Daniel L. Dries, MD, MPH; C.E. Davis, PhD;
Yuan Li Shen, DrPH; Michael J. Domanski, MD

Background—Treatment with diuretics has been reported to increase the risk of arrhythmic death in patients with hypertension. The effect of diuretic therapy on arrhythmic death in patients with left ventricular dysfunction is unknown.

Methods and Results—We conducted a retrospective analysis of 6797 patients with an ejection fraction <0.36 enrolled in the Studies Of Left Ventricular Dysfunction (SOLVD) to assess the relation between diuretic use at baseline and the subsequent risk of arrhythmic death. Participants receiving a diuretic at baseline were more likely to have an arrhythmic death than those not receiving a diuretic (3.1 vs 1.7 arrhythmic deaths per 100 person-years, $P=0.001$). On univariate analysis, diuretic use was associated with an increased risk of arrhythmic death (relative risk [RR] 1.85, $P=0.0001$). After controlling for important covariates, diuretic use remained significantly associated with an increased risk of arrhythmic death (RR 1.37, $P=0.009$). Only non-potassium-sparing diuretic use was independently associated with arrhythmic death (RR 1.33, $P=0.02$). Use of a potassium-sparing diuretic, alone or in combination with a non-potassium-sparing diuretic, was not independently associated with an increased risk of arrhythmic death (RR 0.90, $P=0.6$).

Conclusions—In SOLVD, baseline use of a non-potassium-sparing diuretic was associated with an increased risk of arrhythmic death, whereas baseline use of a potassium-sparing diuretic was not. These data suggest that diuretic-induced electrolyte disturbances may result in fatal arrhythmias in patients with systolic left ventricular dysfunction. (*Circulation*. 1999;100:1311-1315.)

Key Words: diuretics ■ heart failure ■ arrhythmia ■ potassium

Diuretics are used in the treatment of congestive heart failure (CHF), hypertension, and various edematous states. They are among the most frequently prescribed medications, with more than 45 million prescriptions written each year for outpatients alone.¹ Treatment regimens characterized by initial use of these drugs have been shown to reduce overall mortality rates in hypertensive patients.^{2,3} However, the observed reduction in mortality rates has been consistently less than that predicted from epidemiological studies,⁴ raising the possibility that the benefit of blood pressure reduction was partially offset by an adverse effect of these drugs. Subsequent reports have suggested that diuretics increase the risk of arrhythmic death in hypertensive patients, presumably because they alter electrolyte balance.⁵⁻⁹

The potential for deleterious effects of diuretics would appear to be even greater in patients with systolic left ventricular (LV) dysfunction. This is a clinical setting in which electrolyte abnormalities are common, being caused by renal dysfunction, activation of the renin-angiotensin-aldosterone system, and the presence of enhanced sympathetic tone. Electrolyte abnormalities that might be tolerated in patients with a normal heart could

precipitate malignant arrhythmias in patients with LV dysfunction.¹⁰ In addition, the increased risk of arrhythmic death seen with diuretics in hypertensive patients is clearly related to the use of high doses of non-potassium-sparing agents.^{8,11} Patients with systolic LV dysfunction frequently require high-dose diuretics to control congestive symptoms. To study this issue, we performed a retrospective analysis of data from the Studies Of Left Ventricular Dysfunction (SOLVD) to assess the risk of arrhythmic death associated with the use of diuretics in patients with LV dysfunction.

Methods

Study Design

SOLVD has been described in detail elsewhere.¹²⁻¹⁴ Briefly, 6797 patients with known heart disease and an ejection fraction (EF) <0.36 were entered into 1 of 2 trials: the prevention trial, which enrolled 4228 patients without symptomatic heart failure, and the treatment trial, which enrolled 2569 patients with symptomatic heart failure. Patients were randomly assigned to receive enalapril or placebo, with other medications used at the discretion of their treating physicians. Baseline data were obtained regarding comorbid conditions, severity of illness, and concurrent medication use.

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From the Clinical Trials Scientific Research Group, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Md (H.A.C., D.L.D., M.J.D.); the Division of Cardiology, Georgetown University Medical Center, Washington, DC (H.A.C., D.L.D.); and the Department of Biostatistics, University of North Carolina, Chapel Hill (C.E.D., Y.L.S.).

Correspondence to Howard A. Cooper, MD, Clinical Trials Scientific Research Group, National Heart, Lung, and Blood Institute, Two Rockledge Centre, Room 8149, 6701 Rockledge Dr, MSC 7936, Bethesda, MD 20892. E-mail Cooperh@nih.gov

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Participants were followed for an average of 39.9 months. All deaths were reviewed and classified by the principal investigator at the study site. These investigators were blinded to SOLVD treatment assignment but not to concomitant treatments, including diuretic use. Deaths were classified as having a cardiovascular or noncardiovascular cause. Cardiovascular deaths were further classified as being due to arrhythmia without worsening CHF, progressive heart failure with or without an arrhythmia, myocardial infarction (MI), stroke, or other vascular cause. For the purposes of this analysis, arrhythmic death was defined as only those deaths in which the most likely terminal event was a probable arrhythmia without preceding worsening symptoms of CHF.

For this study, data from the prevention and treatment trials were pooled. All analyses are based on therapy at the time of the baseline visit, when a checklist was used to obtain information about medications used by each participant. Patients were included in the non-potassium-sparing diuretic group if they were receiving a loop or thiazide diuretic at baseline and in the potassium-sparing diuretic group if potassium-sparing diuretic treatment was noted at baseline. Patients who were receiving both non-potassium-sparing and potassium-sparing diuretics at baseline were included in the potassium-sparing diuretic group. Only drug class was ascertained; specific medications were not recorded.

The study protocols were approved by the local hospital review boards and the National Heart, Lung, and Blood Institute. All patients enrolled in the SOLVD trials provided written informed consent.

Statistical Analysis

Group comparisons included the 2-sample Student's *t* test for comparison of means and the χ^2 statistic for comparison of proportions. The prognostic significance of each study covariate on the time until arrhythmic death was investigated with the use of univariate and multivariate Cox proportional hazards models. All covariates for which information was available and which were thought to affect the risk of arrhythmic death were included in the multivariate model. These were study drug allocation (enalapril or placebo), age, sex, EF, New York Heart Association (NYHA) class, a history of angina, MI, revascularization, hypertension, diabetes, or tobacco use, or baseline use of digoxin, β -blockers, antiarrhythmic agents, aspirin, or anticoagulants. A 2-sided 95% CI was constructed around the point estimate of relative risk (RR) associated with each study covariate. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS (Statistical Analysis System, version 6.07).

Results

Baseline Characteristics

The baseline characteristics of patients enrolled in SOLVD are presented in Table 1, based on diuretic use. On average, patients receiving diuretics were older, were more likely to be women, and had more indicators of severe heart failure (lower EF, higher NYHA class, and greater use of digoxin) but fewer indicators of ischemic heart disease (angina, prior MI, β -blocker use, or aspirin use). Diuretic users were also more likely to be receiving antiarrhythmic agents and anticoagulants. Table 2 presents detailed information on diuretic class and potassium supplement use at baseline. Forty-three percent of participants were receiving a diuretic at the time of their baseline examination: 37% were receiving only a non-potassium-sparing diuretic and 6% were receiving a potassium-sparing diuretic (1% as the sole diuretic agent, 5% in combination with a non-potassium-sparing diuretic). Twenty-three percent of patients were receiving a potassium supplement at the time of the baseline visit, nearly all of whom were concurrently receiving a non-potassium-sparing diuretic.

TABLE 1. Baseline Characteristics of Participants in SOLVD Prevention and Treatment Trials

	Diuretic (n=2901)	No Diuretic (n=3896)	P
Age	61±9.8	59±10.4	0.0001
Male sex	81	89	0.0001
EF	25±6.7	28±5.7	0.0001
NYHA class III or IV	25	3	0.001
Randomization to enalapril	50	50	0.9
History of			
Angina	55	59	0.002
MI	65	82	0.001
Revascularization	4	3	0.03
Hypertension	51	30	0.001
Tobacco use	76	80	0.001
Diabetes	25	15	0.001
Baseline use of			
Digoxin	73	27	0.0001
β -Blocker	10	23	0.001
Antiarrhythmic agent	20	16	0.001
Aspirin	31	53	0.001
Anticoagulant	13	9	0.001

Data are presented as mean±SD (age, EF) or % of patients (all others).

Distribution of Events by Diuretic Use

Table 3 presents the incidence of death from any cause, cardiovascular death, and arrhythmic death for participants in the SOLVD trials according to diuretic use at baseline. Overall, 27% of deaths were classified as arrhythmic without worsening of heart failure. All-cause and cardiovascular mortality rates were higher in patients receiving a diuretic at baseline. The incidence of arrhythmic death was ≈80% higher in those receiving a diuretic at baseline compared with those not receiving a diuretic.

Univariate Analysis

As shown in Table 4, on univariate Cox analysis the risk of arrhythmic death was significantly higher in patients receiving any diuretic at baseline compared with patients not receiving any diuretic (RR 1.85, 95% CI 1.52 to 2.24, $P=0.0001$). The use of a non-potassium-sparing diuretic was also strongly associated with an increase in the risk of arrhythmic death (RR 1.80, 95% CI 1.48 to 2.18, $P=0.0001$). There was no difference in the risk of arrhythmic death between those patients receiving a potassium-sparing diuretic and those receiving no diuretic (RR 0.86, 95% CI 0.60 to 1.25, $P=0.5$).

Multivariate Analysis

These results are presented in Table 5. After controlling for indicators of disease severity, comorbid illnesses, and concomitant medication use, diuretic use remained significantly associated with arrhythmic death (RR 1.37, 95% CI 1.08 to 1.73, $P=0.009$). Non-potassium-sparing diuretic use was significantly and independently associated with an increased risk of arrhythmic death (RR 1.33, 95% CI 1.05 to 1.69, $P=0.02$). In contrast, potassium-sparing diuretic use was not

TABLE 2. Use of Diuretics and Potassium Supplements at Baseline

	n	Potassium Supplement	No Potassium Supplement	% Receiving Supplement
Any diuretic	2901	1496	1405	52%
Non-potassium-sparing	2495	1441	1054	58%
Potassium-sparing	406	55	351	14%
No diuretic	3896	48	3848	1%
Total	6797	1544	5253	23%

associated with an increased risk of arrhythmic death (RR 0.90, 95% CI 0.61 to 1.31, $P=0.6$).

Effect of ACE Inhibitors on Risk Associated With Diuretics

The relation between diuretics and the risk of arrhythmic death was independent of study drug assignment (enalapril vs placebo) in the multivariate model. In addition, there was no statistical interaction between enalapril use and non-potassium-sparing diuretic use on the risk of arrhythmic death ($P=0.4$), suggesting that there was not a differential impact of non-potassium-sparing diuretics on arrhythmic death in patients who did and those who did not receive enalapril. Finally, in a stratified multivariate analysis, the risk of arrhythmic death associated with diuretic use was not substantially different in those assigned to enalapril (RR 1.40) compared with those assigned to placebo (RR 1.43).

Effect of Potassium Supplements on Risk Associated With Diuretics

There was no statistical interaction between potassium supplementation and non-potassium-sparing diuretic use on the risk of arrhythmic death ($P=0.4$). When baseline use of a potassium supplement was added to the multivariate model, diuretic use remained independently associated with arrhythmic death (RR 1.31, $P=0.04$).

Effect of Diuretics on Serum Potassium

Patients taking a non-potassium-sparing diuretic, when compared with those not taking a non-potassium-sparing diuretic, had lower mean serum potassium levels after adjustment for baseline values (4.32 vs 4.40 mEq/dL, $P<0.0001$). Potassium levels were also lower in individual patients during therapy with a non-potassium-sparing diuretic compared with when they were not receiving such therapy (mean per-patient difference: -0.06 meq/dL, $P<0.0001$).

Discussion

This study demonstrates that the use of non-potassium-sparing diuretics is associated with an increased risk of arrhythmic death

in a large cohort of patients with systolic LV dysfunction. In contrast, the use of potassium-sparing diuretics is not associated with increased arrhythmic death risk when used alone or in conjunction with non-potassium-sparing diuretics.

Comparison With Other Studies

Increased mortality rates associated with non-potassium-sparing diuretic use has been reported in studies of other patient populations, particularly in older studies of blood pressure reduction using high-dose thiazides. The Multiple Risk Factor Intervention Trial Research Group (MRFIT)⁶ randomly assigned patients to usual care or to a special intervention with a diuretic-based stepped-care antihypertensive regimen. In the special intervention group, there was an RR of death of 3.34 for patients with abnormal ECGs who were treated with high-dose diuretics (50 to 100 mg of hydrochlorothiazide or chlorthalidone) compared with those who were not.

In a population-based, case-control study, Siscovick et al⁸ found that the risk of cardiac arrest in patients taking a thiazide diuretic was dose-dependent, with the odds ratio increasing 3.5-fold from the lowest to the highest dose. Further, similar to our study, the risk of cardiac arrest was markedly reduced in patients who were taking a potassium-sparing diuretic in combination with the thiazide diuretic.

In the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension trial),² which included as a primary therapy a combination of a potassium-sparing agent with a thiazide diuretic but not a thiazide diuretic alone, antihypertensive treatment reduced the risk of sudden death 70%. In contrast, the Systolic Hypertension in the Elderly Program (SHEP),¹⁵ which showed that stroke, coronary events, and heart failure incidence in hypertensive patients is improved by diuretic treatment, revealed no effect of thiazide treatment without a potassium-sparing agent on the incidence of sudden cardiac death.

Potential Mechanisms

Given the very large numbers of patients who receive long-term treatment with diuretics, it is important to deter-

TABLE 3. Distribution of Events According to Diuretic Use at Baseline

	Diuretic (n=2901)		No Diuretic (n=3896)		P
	n (%)	Incidence	n (%)	Incidence	
Death from any cause	1013 (34.9)	12.8	586 (15.0)	5.3	0.001
Cardiovascular death	903 (31.1)	11.4	510 (13.1)	4.6	0.001
Arrhythmic death	241 (8.3)	3.1	183 (4.7)	1.7	0.001

Incidence is expressed as number of events per 100 patient-years of follow-up.

TABLE 4. Univariate Analysis: Relative Risk of Arrhythmic Death According to Diuretic Use

	RR (95% CI)*	P
No diuretic	1.00	...
Any diuretic	1.85 (1.52-2.24)	0.0001
Non-potassium-sparing diuretic	1.80 (1.48-2.18)	0.0001
Potassium-sparing diuretic	0.86 (0.60-1.25)	0.5

Participants receiving no diuretic were chosen as reference group in calculating RR.

*Two-sided 95% CI.

mine which patient characteristics might identify a group at increased risk for arrhythmic death and which adjunctive therapy might reduce this risk.

Patients with structurally abnormal hearts are at increased risk for ventricular arrhythmias and are likely to be at particular risk for complications from diuretic therapy. SOLVD selected patients with known systolic LV dysfunction. In MRFIT, the increased risk of sudden cardiac death in patients receiving diuretics was seen only in patients with abnormal ECGs.⁶ In such high-risk, middle-aged men, an abnormal ECG likely identifies a group with a high prevalence of structural heart disease. The case-control study by Siscovick et al⁸ attempted to exclude patients with clinically recognized heart disease on the basis of review of computerized records. It is likely, however, that a significant number of these middle-aged, predominately male, hypertensive patients, 30% of whom were current smokers and 11% of whom were diabetic, had heart disease that was unrecognized or not recorded in the database.

Pathophysiological data exist to support a link between diuretic therapy and an increase in arrhythmic death in patients with structural heart disease based on electrolyte depletion. Non-potassium-sparing diuretics reduce serum and total-body potassium and magnesium in a dose-dependent fashion,¹⁶⁻¹⁸ and significant hypokalemia is not unusual.¹⁹ Indeed, we have demonstrated that in SOLVD, non-potassium-sparing diuretics were associated with lower serum potassium levels. Other research has demonstrated that hypokalemia and hypomagnesemia predispose to ventricular ectopic activity.^{19,20} In patients with CHF or recent MI, this relation is particularly evident.²¹⁻²³ Ventricular ectopy, in turn, is a strong predictor of arrhythmic death in patients with structural heart disease.^{24,25}

TABLE 5. Multivariate Analysis: Relative Risk of Arrhythmic Death According to Diuretic Use

	RR (95% CI)	P
No diuretic	1.00	...
Any diuretic	1.37 (1.08-1.73)	0.009
Non-potassium-sparing diuretic	1.33 (1.05-1.69)	0.02
Potassium-sparing diuretic	0.90 (0.61-1.31)	0.6

The multivariate Cox model also included study drug allocation (enalapril or placebo); age; sex; EF; NYHA class; history of angina, MI, revascularization, hypertension, diabetes, or tobacco use; and baseline use of digoxin, β -blockers, antiarrhythmic agents, aspirin, or anticoagulants.

If potassium depletion is the cause of arrhythmic death in some patients receiving diuretic therapy, then potassium-sparing diuretics would not be expected to increase the risk of arrhythmic death. Our data bear this out: we found no association between potassium-sparing diuretic use and the risk of arrhythmic death in SOLVD participants. This is despite the fact that most of these patients were receiving a combination of non-potassium-sparing diuretics and potassium-sparing diuretics, which would tend to increase the association with arrhythmic death. We did not attempt to analyze potassium-sparing diuretics alone because numbers were too small to reach any reasonable conclusion in this group. The results of several previous studies bear on the use of potassium-sparing diuretics in patients with LV dysfunction. The Xamoterol in Severe Heart Failure trial²⁶ of 516 patients with NYHA class III or IV heart failure randomly assigned participants to xamoterol or placebo and followed them for 100 days. All participants were receiving therapy with diuretics and an ACE inhibitor. A retrospective analysis revealed that the mortality rate was lower in participants receiving potassium-sparing diuretics compared with those not receiving these drugs (4.6% vs 8.5%), although this difference did not achieve statistical significance ($P=0.1$). Barr et al²⁷ randomly assigned 42 patients with NYHA class II or III heart failure who were receiving treatment with loop diuretics and an ACE inhibitor to the potassium-sparing diuretic spironolactone or matching placebo for 8 weeks. A significant reduction in the number of ventricular ectopic beats on Holter monitoring was seen in the participants receiving spironolactone compared with those receiving placebo.²⁷ Finally, the Randomized Aldactone Evaluation Study Parallel Dose Finding Trial²⁸ demonstrated that the addition of spironolactone to a loop diuretic and an ACE inhibitor was well tolerated and significantly decreased the risk of hypokalemia.

Both ACE inhibitors and potassium supplements might be expected to reduce the incidence of hypokalemia in patients receiving non-potassium-sparing diuretics. Despite this, we found no substantial alteration in the risk of arrhythmic death associated with diuretic use by either of these agents. Therefore we must postulate that neither ACE inhibitors nor potassium supplements in the doses used in SOLVD patients provided consistent protection from the deleterious effects of non-potassium-sparing diuretic use.

Clinical Implications

On the basis of the results of our analysis and the other studies cited above, we believe that several interventions to reduce the risk of arrhythmic death should be considered in patients with systolic LV dysfunction. The minority of patients without volume overload or hypertension after treatment with an ACE inhibitor may not require a diuretic. Some patients with mild volume overload may be satisfactorily treated with a potassium-sparing agent alone. In the majority of patients who require loop or thiazide diuretics to relieve congestive symptoms, the minimum effective dose should be used. In addition, those with normal renal function may benefit from the routine addition of a potassium-sparing agent. The impact of this last strategy on survival in patients with severe heart

failure will be determined by the recently completed Randomized Aldactone Evaluation Study.²⁹ Finally, all patients with LV dysfunction who are receiving diuretics should have their serum electrolytes monitored on a regular basis, and aggressive supplementation should be provided as needed.

Study Limitations

The SOLVD trials were not randomized studies of the risk of arrhythmic death caused by diuretics. However, the SOLVD database contained detailed information on disease severity, comorbid illnesses, and concomitant medication use. All factors that were considered possible confounders were controlled for in our multivariate analysis. The existence of additional, unrecognized confounding factors cannot be excluded.

A significant limitation of the current study is the absence of information on diuretic dosage. The hypertension literature strongly suggests that only high-dose diuretic therapy has a negative impact on arrhythmic death. Without this information, we could not reach any conclusions regarding a dose-effect relation in the SOLVD population. An additional limitation is that diuretic use was analyzed on the basis of reported use at the baseline study visit. Diuretic status may have changed through the course of the study, an occurrence we could not account for in our analysis. However, changes in diuretic therapy for participants throughout the course of the study would tend to make the 2 groups more similar and bias the results toward the null hypothesis. Therefore the positive findings of the current study argue strongly in favor of a true association between diuretic use and arrhythmic death.

Conclusions

The use of non-potassium-sparing but not potassium-sparing diuretics is associated with an increased risk of arrhythmic death in patients with systolic LV dysfunction. The combination of a potassium-sparing diuretic with a non-potassium-sparing diuretic is not associated with an increased risk of arrhythmic death. These data implicate diuretic-induced potassium depletion as a cause of arrhythmic death in patients with systolic LV dysfunction and suggest that the use of a potassium-sparing diuretic should be considered when diuretic therapy is required. Further, potassium-sparing diuretics may be protective when a non-potassium-sparing diuretic is needed; clarification of the impact of this strategy on death, at least in patients with severe heart failure, awaits the results of a recently completed clinical trial. Finally, careful monitoring of serum potassium is essential in all patients receiving non-potassium-sparing diuretics.

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